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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
PATENT EXAMINING OPERATION

Applicant(s): Glen H. ERIKSON et al.

Serial No: 09/664,827 Group Art Unit: 1637

Filed: September 19, 2000 Examiner: S. Chunduru

Att. Docket No.: E1047/20044 Confirmation No.: 4947

For: QUADRUPLEX DNA AND DUPLEX PROBE SYSTEMS

REQUEST FOR RECONSIDERATION AFTER FINAL REJECTION

Box AF
Commissioner for Patents
Washington, DC 20231

Sir:

In response to the Final Rejection dated May 30, 2002, favorable reconsideration is respectfully requested in view of the following remarks.

Claims 1-52 are pending, with claims 26-49 and 52 being withdrawn from consideration pursuant to a restriction requirement.

Applicants gratefully acknowledge the withdrawal of all the prior art related rejections.

Claims 1-25 and 50-51 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing non-enabled subject matter. This rejection is respectfully traversed.

An invention is patentably enabled if one of ordinary skill in the art could make or use the invention from the disclosures in the patent application coupled with information known in the art without undue experimentation. See, e.g., MPEP § 2164.01 citing *United States v. Telecommunications, Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988).

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The first step in an enablement analysis is to construe the claims. MPEP § 2164. Claim 1 specifies a multiplex structure comprising four strands, wherein the first strand is associated with the second strand by Watson-Crick bonding, and the fourth strand is associated with the second strand and the third strand by Watson-Crick bonding. In addition, at least one nucleobase of the fourth strand is associated by Watson-Crick bonding to at least one nucleobase of the third strand and to at least one nucleobase of the second strand. The meaning of Watson-Crick bonding in the context of the invention is provided in the application at page 5, lines 25-33:

As used herein, the term "Watson-Crick bonding" is intended to define specific association between opposing pairs of nucleic acid (and/or nucleic acid analogue) strands via matched, opposing bases. While the formation of a Watson-Crick quadruplex may sometimes be referred to as a hybridization event herein, that is merely for convenience and is not intended to limit the scope of the invention with respect to how the formation of a Watson-Crick quadruplex can be best characterized.

It should be clear from the foregoing that base claim 1 and the claims dependent therefrom are directed to a quadruplex of four nucleobase-containing strands, wherein Adenines align with Thymines (or Uracils) and Cytosines align with Guanines. Although the original disclosure does not explicitly disclose the interatom hydrogen bond locations, distances and quantities like those of

duplex DNA figure in the Final Rejection at pages 4-5, such additional information is not necessary to "make or use" the claimed invention, which does not specify such nanoscale features of the invention. The working examples of the specification (which are improperly overlooked in the Final Rejection, which points to "the absence of any working examples" at page 9, line 9) show that Applicants were able to make and use the invention without undertaking detailed biophysical studies. See the attached Rule 132 Declaration of Dr. J. Hans van de Sande (hereinafter the "JHS Declaration") at, e.g., paragraph 7. Likewise, one of ordinary skill in the art (whom the Final Rejection acknowledges has a high level of skill) would be able to make and use with no more than routine experimentation the claimed multiplexes for purposes such as assays without ever knowing for certain the location, length and/or number of hydrogen bonds between adjacent bases in the multiplex. See the JHS Declaration at, e.g., paragraph 10.

Applicants have shown specific association of non-denatured dsDNA targets with non-denatured dsDNA probes. The targets and probes align Adenine to Thymine (or Uracil) and Cytosine to Guanine. In light of Applicants' evidence that two strands on opposing non-denatured duplexes specifically interact together A:T(U) and C:G, one of ordinary skill in the art would have found it reasonable to infer that adjacent bases in the remaining two strands of the duplexes would be brought into close enough

proximity by the initial pairing of opposing strands to specifically interact together A:T(U) and C:G. JHS Declaration at paragraphs 8-9. This inference would not have been considered by an ordinarily skilled artisan to be a direct affront to the conventional understanding of Watson-Crick bonding, so much as a reasonable corollary of the paradigm-shifting evidence of specific binding between non-denatured duplexes of mixed bases. JHS Declaration at paragraphs 8-9. See also the inventors' U.S. Patents Nos. 6,420,115 to Erikson et al., 6,403,313 to Daksis et al. and 6,265,170 to Picard et al., each of which provides additional evidence (in the form of Watson-Crick triplex binding studies) that the conventional understanding of Watson-Crick bonding is incomplete and should not be accorded the stature of an immutable truth in evaluating the enablement and credible utility of this invention. Thus, the high level of evidence being required by the Patent Office for this invention is directly met by the working examples, which show non-denatured quadruplex binding complexes, and Applicants should not be required to make an additional or equally burdensome showing regarding additional details irrelevant to making or using the invention.

Furthermore, Professor van de Sande cites an article (attached to his Declaration as Exhibit B) published subsequent to the filing of this application, which disproves the theory in the Final Rejection at page 6, last sentence, that "Watson-crick hydrogen

bonding surfaces are inaccessible for any other strands [i.e., strands other than the two hybridized strands of conventional duplexes] since two strands are already interacting with each other at the center of the double helix." Zhang et al., "Dimeric DNA Quadruplex Containing Major Groove Aligned A•T•A•T and G•C•G•C Tetrads Stabilized by Inter-subunit Watson-Crick A•T and G•C Pairs," 312 J. Mol. Biol. 1073-88 (Oct. 5, 2001), shows through NMR studies the formation of A-T-A-T tetrads similar to previously discovered G-C-G-C tetrads. Zhang et al. at pages 1073-74 states:

[E]fforts have been made to identify and characterize G•C•G•C tetrads, where a pair of Watson-Crick G•C pairs can potentially align either through their major groove or their minor groove edges. . . . recent studies have demonstrated that G•C•G•C tetrads aligned through their major groove edges can switch between two distinct alignment geometries [shown in Figure 1(a) and 1(b)]. . . . The major groove-aligned G•C•G•C tetrad has now been observed in a range of DNA quadruplexes and appears to be a robust tetrad motif adopted by a wide range of DNA sequences.

Figure 1 of Zhang et al. shows how major groove-aligned G•C•G•C and A•T•A•T tetrads in their direct alignment geometry have each G hydrogen bonded to each C, and each A hydrogen bonded to each T. Thus, contrary to the Final Rejection, Zhang et al. and the art cited therein (whether prior or not) shows that quadruplex G-C-G-C and A-T-A-T binding is reasonably credible. JHS Declaration at paragraphs 8-9.

In summary, it should be apparent that the claimed invention is patentably enabled when the Wands Factors are properly applied. Contrary to the Final Rejection at page 9, line 10, the high skill level in the art is not the only factor favoring Applicants. Firstly, along with a high level of skill comes a high tolerance of experimental complexity. Secondly, the art does recognize the existence of quadruplex G-C-G-C and A-T-A-T binding. Thirdly, working examples are present in the original disclosure, despite the assertion to the contrary in the Final Rejection at page 9, line 9. The fact that the Office might prefer working NMR or crystallographic examples is no basis for completely ignoring the evidentiary weight of the extensive binding studies in the application, particularly in view of the JHS Declaration's explanation of the significance of the binding studies. Moreover, the working examples provided are much more relevant to "making and using" the claimed invention than the requested biophysical studies, as suggested by the JHS Declaration at paragraph 10.

Accordingly, reconsideration and withdrawal of the non-enablement rejection are respectfully requested.

Claims 1-25 and 50-51 stand rejected under 35 U.S.C. § 101, as allegedly lacking patentable utility. This rejection is respectfully traversed.

The stated basis for this rejection is set forth in the Final Rejection at page 10, lines 2-5, as follows:

[T]he basic multiplex structure involving Watson-Crick base pairing with more than two strands is incredible and use of such structure is incredible based on unpredictability of the multiplex structure involving Watson-Crick pairing with more than two strands, as discussed above in the enablement rejection.

According to MPEP § 2107.02:

To properly reject a claimed invention under 35 U.S.C. 101, the Office must (A) make a *prima facie* showing that the claimed invention lacks utility, and (B) provide a sufficient evidentiary basis for factual assumptions relied upon in establishing the *prima facie* showing. *In re Gaubert*, 524 F.2d 1222, 1224, 187 USPQ 664, 666 (CCPA 1975).

The Final Rejection fails to make a *prima facie* showing under 35 U.S.C. § 101, because the factual assumptions underlying the purported showing are incorrect and incomplete, as shown above with respect to the non-enablement rejection.

Working examples are provided in the specification, but improperly overlooked in the Final Rejection. If the Office maintains that the working examples do not substantiate the existence of quadruplexes, it must provide “[a]n explanation that clearly sets forth the reasoning used in concluding that the asserted specific and substantial utility is not credible.” MPEP § 2107.02. The Final Rejection does not even attempt to show that the working examples are unreliable or irrelevant to the credible utility of the claimed invention.

It was Supervisory Examiner Fredman's theory at the January 15, 2002 interview that the working examples could merely be an example of strand invasion that has been misinterpreted by the inventors. This theory was refuted by Jasmine Daksis in her Rule 132 Declaration of January 18, 2002. Neither this theory, nor any alternative theory explaining away Applicants' working examples, is suggested in the Final Rejection.

Even if the Office had made a *prima facie* showing, the showing is rebutted by Applicants' showing, including the attached Declaration of Professor van de Sande, wherein the Professor describes through well-reasoned logic and supporting evidence how one of ordinary skill in the art would find the claimed invention to be reasonably credible. The art recognizes the existence of quadruplex G-C-G-C and A-T-A-T binding, contrary to the assertion in the Final Rejection.

Accordingly, reconsideration and withdrawal of the utility rejection are respectfully requested.

For at least the reasons set forth above, it is respectfully submitted that the above-identified application is in condition for allowance. Favorable reconsideration and prompt allowance of the claims are respectfully requested.

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Should the Examiner believe that anything further is desirable in order to place the application in even better condition for allowance, the Examiner is invited to contact Applicants' undersigned attorney at the telephone number listed below.

Respectfully submitted,

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September 27, 2002

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